

Fingolimod (Gilenya®)**Criteria for Use**

VHA Pharmacy Benefits Management Services, Medical Advisory Panel and VISN Pharmacist Executives

The following recommendations are based on medical evidence, clinician input, and expert opinion. The content of the document is dynamic and will be revised as new information becomes available. The purpose of this document is to assist practitioners in clinical decision-making, to standardize and improve the quality of patient care, and to promote cost-effective drug prescribing. **THE CLINICIAN SHOULD UTILIZE THIS GUIDANCE AND INTERPRET IT IN THE CLINICAL CONTEXT OF THE INDIVIDUAL PATIENT. INDIVIDUAL CASES THAT ARE EXCEPTIONS TO THE EXCLUSION AND INCLUSION CRITERIA SHOULD BE ADJUDICATED AT THE LOCAL FACILITY ACCORDING TO THE POLICY AND PROCEDURES OF ITS P&T COMMITTEE AND PHARMACY SERVICES.**

The Product Information should be consulted for detailed prescribing information.

See the VA National PBM-MAP-VPE Monograph on this drug at www.pbm.va.gov or <http://vawww.pbm.va.gov> for further information.

Exclusion Criteria (if any box is checked the patient DOES NOT qualify for fingolimod)

- ☐ Primary progressive multiple sclerosis
- ☐ Secondary progressive MS and no clinical or MRI evidence of relapses
- ☐ Concurrent use of immune system modifying drugs (DMT) to treat MS (i.e.; interferon beta-1B, glatiramer acetate, interferon beta 1A, natalizumab, mitoxantrone) unless the previous agent will be discontinued when fingolimod is initiated.
- ☐ Evidence of macular edema on ophthalmologic exam (see monitoring section)
- ☐ Patients who in the last 6 months experienced myocardial infarction, unstable angina, stroke, TIA, decompensated heart failure (requiring hospitalization or Class III/IV heart failure)
- ☐ Mobitz Type II second-degree or third-degree atrioventricular (AV) block or sick sinus syndrome, unless patient has a functioning pacemaker
- ☐ Baseline QTc interval ≥ 500 ms
- ☐ Treatment with Class Ia or Class III anti-arrhythmic drugs
- ☐ Concurrent therapy with drugs that slow heart rate (e.g., beta blockers, heart-rate lowering calcium channel blockers such as diltiazem or verapamil, or digoxin) may be associated with severe bradycardia or heart block. The possibility to switch to non-heart-rate lowering drugs should be evaluated by the physician prescribing the heart-rate lowering drug before initiating fingolimod.
- ☐ No documented baseline testing including (within 30 days prior to fingolimod); CBC with differential, LFT, EKG and skin exam.

Inclusion Criteria

Patient with relapsing MS^a characterized by disease activity defined as one or more relapses in the past two years prior to therapy or gadolinium positive lesions on MRI^b, or new T2 lesions on MRI

AND

- ☐ Loss of clinical response to disease modifying therapy (interferon beta 1a, interferon beta 1b or glatiramer)

OR

- ☐ Acquired intolerance to therapy with glatiramer, interferon beta 1a or interferon beta 1b or natalizumab

OR

- ☐ Currently on natalizumab therapy with development of risk factors for PML (duration of therapy > 24 months, anti JC virus antibody positive or received immunosuppressant therapy prior to natalizumab)

An appropriate washout time from previous DMT is unknown. Currently available evidence demonstrates that relapse rates are not higher in patients with multiple sclerosis switching to fingolimod from natalizumab compared to those patients switching to fingolimod from other therapies. Additionally, retrospective data demonstrated patients switched to fingolimod had fewer relapses than those switched to glatiramer. Various time periods have been reported, from 2 weeks- 6 months. In patients who have received prior DMT agents, a baseline MRI is recommended prior to initiating fingolimod. The risks of a longer washout period should be weighed against the risks of another relapse.

Dosage Recommendations

- Fingolimod is dosed 0.5 mg ,orally once daily
- There is no dosage adjustment based on renal function or in mild to moderate hepatic impairment.
- Ketoconazole may increase fingolimod blood concentrations by 1.7-fold when given concomitantly, increasing the risk of potential adverse reactions.

Issues for Consideration

- Patients without a documented history of varicella zoster virus infection or vaccination against it should be evaluated for vaccination against varicella prior to fingolimod initiation. Zostavax® should not be used in these individuals. In these patients vaccination with the live varicella virus product (Varivax®) should be undertaken and these patients should not initiate fingolimod therapy until at least one month after the two doses of vaccine are completed. Consult the CDC website for guidance. (2 doses of the vaccine must be given at least 4 weeks apart) www.cdc.gov/vaccines/recs/schedules/adult-schedule.htm
- Fingolimod is a pregnancy Category C medication. Elimination of fingolimod can take up to 2 months following discontinuation of the drug. Women of child bearing potential should be counseled regarding appropriate forms of contraception during this period.
- Dose dependent reductions of FEV1 and diffusion lung capacity for carbon monoxide have been observed. Evaluation of these parameters should be conducted as clinically indicated.
- Fingolimod has been associated with development of melanomas although the risk does not appear greater than the general

population. Referral of high risk individuals to dermatology may be considered.

- The use of live vaccines after initiation of fingolimod therapy should be discouraged (<http://www.fda.gov/BiologicsBloodVaccines/Vaccines/ApprovedProducts/ucm093833.htm>)
- If fingolimod therapy is discontinued for more than 14 days, after the first month of treatment, the effects on heart rate and AV conduction may recur on reintroduction of treatment and the same precautions (first dose monitoring) would apply. Within the first 2 weeks of treatment, first dose procedures are recommended after interruption of one day or more, during week 3 and 4 of treatment first dose procedures are recommended after treatment interruption of more than 7 days

Monitoring

- The first dose of fingolimod should be administered in a setting in which resources to appropriately manage symptomatic bradycardia are available. In order to assess patient response to the first dose of fingolimod, observe all patients for 6 hours for signs and symptoms of bradycardia with hourly pulse and blood pressure measurement. Obtain in all patients an electrocardiogram prior to dosing, and at the end of the observation period.
- After the first dose of fingolimod, heart rate decrease can start within an hour. This is followed by a maximal decline in heart rate within 6 hours. Heart rate recovers, although not to baseline levels, by 8-10 hours post dose. Because of physiological diurnal variation, a second period of heart rate decrease may begin within 24 hours after the first dose. In some patients, this decrease in heart rate may be more pronounced than the decrease observed in the first 6 hours.
- Patients with bradycardia risk factors (age > 70 yrs, MI in the past 12 months, hypothyroidism, sleep apnea or electrolyte disorder) should undergo cardiology evaluation before considering treatment. If treatment is initiated, the first dose should be undertaken with EKG monitoring that is continued for at least 24 hours. Total duration of EKG monitoring should be determined in consultation with the cardiologist.
- Additional observation should be instituted until the finding has resolved in the following situations:
 - The heart rate 6 hours post-dose is < 45 bpm
 - The heart rate 6 hours post-dose is at the lowest value post-dose (suggesting that the maximum pharmacodynamics effect on the heart may not have occurred and continuation of monitoring may be necessary)
 - The ECG 6-hours post-dose shows new onset second degree or higher AV block
- Should post-dose symptomatic bradycardia occur, initiate appropriate management, begin continuous ECG monitoring and continue observation until the symptoms have resolved.
- Should a patient require pharmacologic intervention for symptomatic bradycardia, continuous overnight ECG monitoring in a medical facility should be instituted, and the first dose monitoring strategy should be repeated after the second dose of fingolimod
- Since initiation of fingolimod treatment results in decreased heart rate and may prolong the QT interval, patients with a prolonged QT interval (> 450 msec males, > 470 msec females) before dosing or during 6 hour observation, or at additional risk for QT prolongation (e.g., hypokalemia, hypomagnesemia, congenital long-QT syndrome, concurrent therapy with QT prolonging drugs) should be monitored overnight with continuous ECG in a medical facility
- Patients with diabetes mellitus and/or uveitis may be at an increased risk for macular edema. Ophthalmology evaluation repeated 3- 4 months after fingolimod initiation with subsequent evaluations based on clinical symptoms is warranted.
- CBC and LFT's (liver transaminases) repeated at 3-6 month intervals. Fingolimod should be discontinued in patients who develop elevation of LFT 5X the ULN
- An annual brain MRI by CMSC Protocol (www.va.gov/ms) is recommended

* Relapsing Forms of MS include: **Relapsing, remitting MS:** A clinical course of MS characterized by clearly defined, acute attacks with full or partial recovery and no disease progression between attacks. **Secondary progressive MS with superimposed relapses:** A clinical course of MS that shows steady progression but with superimposed acute relapses, after an initial relapsing-remitting course, **Progressive-relapsing MS:** A clinical course of MS that shows disease progression from the beginning, but with clear, acute relapses, with or without full recovery from those relapses.^b gadolinium should not be used in patients with CrCl ≤ 30 ml/min or those on dialysis